known. For example, it is stable indefinitely in air, and it does not lose O_2 by pumping at 80° and 0.05 Torr. However, it does react rapidly with other chemicals such as sulfur dioxide. Bubbling SO_2 through a suspension of $RhLCl \cdot O_2$ in benzene immediately converts the dioxygen complex into the yellow sulfate complex of Rh(III), $RhLCl \cdot SO_4$. The infrared spectrum of the latter complex exhibits strong peaks at 1250, 1240, 1147, and 640 cm^{-1}, characteristic of a bidentate sulfate group,[10] while the 862-cm^{-1} peak due to the symmetric

unit[11] in $RhLCl \cdot O_2$ has disappeared. If one performs the SO_2 and O_2 reactions in the reverse manner, *i.e.*, by bubbling O_2 through a benzene solution of $RhLCl \cdot SO_2$, no sulfate complex is formed within 1 hr at 25°. Thus, the addition sequence of reagents is very important in forming the $RhLCl \cdot SO_4$ complex. Collman found that the $Ir(Ph_3P)_3Cl \cdot O_2$ complex also reacts with SO_2 much faster than the corresponding SO_2 complex reacts with molecular oxygen.[12]

The disulfur complex $\mathbf{1} \cdot S_2$ was isolated by treating a benzene slurry of **1** with a benzene solution of cyclooctasulfur. This reaction could conceivably convert two of the three phosphine donors in L to phosphine sulfide groups. In fact, the analytical data and the infrared spectrum, which shows a new peak at 546 cm^{-1}, would be consistent with a complex containing two coordinated phosphine sulfide groups. However, such a complex can be excluded on the basis of the mass spectrum of $RhLCl \cdot S_2$, which shows the peak of highest relative abundance at m/e = 700 (*i.e.*, $RhL^{35}Cl$) and no peaks attributable to phosphine sulfide fragments. Thus, the S_2 group is not incorporated into the triphosphine ligand, and we propose that $\mathbf{1} \cdot S_2$ contains a symmetrically, π-bonded S_2 ligand similar to the recently prepared iridium complex $[Ir(diphos)_2S_2]Cl \cdot CH_3CN$ (diphos = bis(diphenylphosphino)ethane).[6,13] The RhLCl compound has cleaved the S_8 ring during the reaction and stabilized the S_2 fragment, which does not exist at room temperature.

Five-coordinate cationic complexes of the general formulas $[RhLCl \cdot A]^+$ (A = H, NO, N_2Ph) may be isolated by treating RhLCl with cationic reagents such as H^+, NO^+, and $N{\equiv}NPh^+$. For example, the cationic hydride $[RhLClH]^+$, which has νRh–H at 2198 cm^{-1} (Nujol), was isolated by treating RhLCl with aqueous 50% HBF_4. The nitrosyl cation $[RhLClNO]^+$ is obtained from RhLCl and $NO^+BF_4^-$ in a benzene–methanol mixture. The NO stretching frequency (1699 cm^{-1}) is in the range for a bent Rh–N–O linkage.[14] The phenyl diazonium cation, $C_6H_5N_2^+$, reacts with **1** to form the phenylazo complex $[\mathbf{1} \cdot N_2C_6H_5]BF_4$. The red-orange crystals separate from the methanol reaction solution at or slightly below room temperature; however, if this slurry is warmed to *ca.* 50°, the red-orange crystals redissolve and the solution turns golden yellow. The hydride $[\mathbf{1} \cdot H]BF_4$ can be isolated from this yellow solution in good yield. Anisole, $C_6H_5OCH_3$, was identified by glc as a major product of this decomposition.

Four- and five-coordinate cations of the types $[RhL(solvent)]^+$, $[RhLCO]^+$, $[RhL(solvent)A]^+$, and $[RhL(CO)_2]^+$ can be obtained by chloride displacement from RhLCl in polar solvents. Several of these four- and five-coordinate cations are interconvertible, depending on the reaction conditions. For example, the dicarbonyl $[RhL(CO)_2]PF_6$ is isolated from a 1:1 dichloromethane–acetone mixture when the solution is saturated with CO; however, the monocarbonyl $[RhLCO]PF_6$ is isolated if the solution is treated with CO and then purged with N_2. The infrared spectrum of freshly prepared solid $[RhL(CO)_2]PF_6$ shows two strong, sharp peaks at 2037 and 1980 cm^{-1}. The compound loses carbon monoxide over a period of weeks in the solid state and rapidly with effervescence in solution to give the monocarbonyl cation $[RhLCO]^+$, which has one infrared peak in the CO region at 2026 cm^{-1} (CH_2Cl_2). If a solution containing $[RhLCO]^+$ is saturated with CO at 1 atm and 25°, the $[RhL(CO)_2]^+$ cation can be isolated.

On the basis of the increased stability and reactivity patterns of these four- and five-coordinate rhodium complexes of the chelating triphosphine $C_6H_5P[CH_2CH_2CH_2P(C_6H_5)_2]_2$ as compared to other tertiary phosphine–rhodium systems, it is concluded that the RhLCl complex offers tremendous potential for future study because (1) in general, it functions as a stronger Lewis base; (2) it forms qualitatively more stable adducts of small molecules (*cf.* the increased stability of the O_2, SO_2, and BF_3 adducts); and (3) it simplifies the stoichiometry of the products, as all three phosphine groups remain bonded in the resulting complexes.

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(10) J. J. Levison and S. D. Robinson, *J. Chem. Soc. A*, 762 (1971).
(11) J. A. McGinnety, N. C. Payne, and J. A. Ibers, *J. Amer. Chem. Soc.*, **91**, 6301 (1969).
(12) J. Valentine, D. Valentine, Jr., and J. P. Collman, *Inorg. Chem.*, **10**, 219 (1971).
(13) W. D. Bonds and J. A. Ibers, presented at the 162nd National Meeting of the American Chemical Society, Washington, D. C., Sept 1971, Abstracts, No. INORG 156.
(14) D. J. Hodgson and J. A. Ibers, *Inorg. Chem.*, **7**, 2345 (1968); **8**, 1282 (1969); D. M. P. Mingos and J. A. Ibers, *ibid.*, **9**, 1105 (1970).

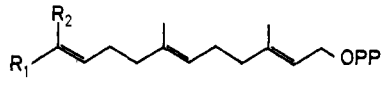
Enzymic Formation of Squalene Homologs from Farnesyl Pyrophosphate Homologs

Sir:

The effect of structural modification of 2,3-oxidosqualene on the enzymic cyclization has been studied in some detail.[1] The substrate specificity of the "head-to-tail" condensation catalyzed by farnesyl-PP[2] synthetase has also been studied.[3,4] However, the specificity of the "tail-to-tail" condensation of farnesyl-PP, *i.e.*, the formation of squalene, has not yet been reported. We describe here the finding that 12-methyl-

(1) E. E. van Tamelen, *Accounts Chem. Res.*, **1**, 111 (1968); E. J. Corey, K. Lin, and H. Yamamoto, *J. Amer. Chem. Soc.*, **91**, 2132 (1969), and references cited in these papers.
(2) PP stands for pyrophosphate.
(3) G. Popják, J. L. Rabinowitz, and J. M. Baron, *Biochem. J.*, **113**, 861 (1969).
(4) K. Ogura, T. Nishino, T. Koyama, and S. Seto, *J. Amer. Chem. Soc.*, **92**, 6036 (1970).

(1) and 12′-methylfarnesyl-PP (2) undergo the dimeric condensation by the action of pig liver microsomal enzyme to give squalene homologs, whereas ethyl derivatives 3 and 4 were inactive to such condensation.



1 : $R_1=C_2H_5$, $R_2=CH_3$
2 : $R_1=CH_3$, $R_2=C_2H_5$
3 : $R_1=n\text{-}C_3H_7$, $R_2=CH_3$
4 : $R_1=CH_3$, $R_2=n\text{-}C_3H_7$

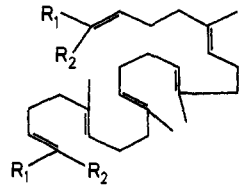
Radiolabeled homologs of farnesyl-PP were synthesized by the incubation of [^{14}C]isopentenyl-PP and an appropriate homolog of dimethylallyl-PP with farnesyl-PP synthetase of pumpkin by the method similar to that previously reported.[4] The separation of the radioactive farnesyl-PP homologs from [^{14}C]-isopentenyl-PP and enzyme protein was performed by chromatography on Sephadex G-10 with 0.05 *M* phosphate buffer, pH 7.0. Farnesyl-PP and its homologs were found to move abnormally slowly on Sephadex G-10, and hence this property was convenient for the purification of the farnesyl-PP analogs. Since the farnesyl-PP synthetase preparation was free from isopentenyl-PP isomerase, the specimens of the [^{14}C] homologs thus obtained contained no detectable amount of [^{14}C]farnesyl-PP which might be an obstacle to the present study. The absence of [^{14}C]farnesyl-PP and [^{14}C]isopentenyl-PP in the specimen was confirmed by tlc and radio-gas chromatography of the free alcohols derived from the homologs by phosphatase treatment.

The standard incubation mixture for the dimeric condensation contained, in a final volume of 2 ml, 200 μmol of phosphate buffer, pH 7.4, and [^{14}C]farnesyl-PP homolog (specific activity, 2.4 μCi/μmol) in the amounts indicated: 1.5 μmol of NADH; 6 μmol of nicotinamide; 10 μmol of $MgCl_2$; 20 μmol of KF; and 0.2 ml of doubly washed microsomes prepared from pig liver homogenate.[5] The incubation was carried out anaerobically at 37° for 2 hr, and the nonsaponifiable materials were extracted with light petroleum in the usual way. The radioactive materials in the extracts were chromatographed on tlc in two different solvent systems, and the location and the amount of the radioactivity were determined. Table I shows these results.

Table I. Conversion of Farnesyl-PP Homologs to Nonsaponifiable Materials

Starting substrate, 10^3 dpm	Nonsaponifiable material, 10^3 dpm	
	Hydrocarbon	Alcohol
12-Methylfarnesyl-PP (1), 50	22.0	4.4
12′-Methylfarnesyl-PP (2), 50	16.2	5.1
12-Ethylfarnesyl-PP (3), 50	0.0	28.1
12′-Ethylfarnesyl-PP (4), 50	0.0	26.6
Farnesyl-PP, 50	27.0	0.9

Approximately 83% of the radioactivity in the nonsaponifiable fraction derived from 1 was found to be associated with a material closely resembling squalene. The radioactive material had the same R_f (0.88) as that of squalene in a system of benzene–ethyl acetate (9:1) but it showed a slightly larger R_f (0.74) than squalene (0.71) in *n*-hexane–benzene (9:1). The rest of the radioactivity in the nonsaponifiable fraction was associated with 12-methylfarnesol (R_f, 0.54 in the former and 0.03 in the latter system). The radioactive material appearing around R_f 0.74 in the *n*-hexane–benzene system was extracted from the tlc plate and subjected to radio-gas chromatography.[6] The retention volume of this radioactive material relative to that for squalene on 2% OV-17 was 1.63, excluding a possibility of the formation of C_{16}-hydrocarbon such as homofarnesene. In order to obtain this squalene-like hydrocarbon in sufficient quantity for analysis by glpc–mass spectrometry, an incubation of 20 times scale was carried out using nonlabeled isopentenyl-PP. The hydrocarbon fraction purified on tlc was subjected to glpc–mass spectrometry.[7] The glpc showed two peaks, one (A) at 6.0 min and the other (B) at 9.8 min with nearly equal intensity. The mass spectrum for peak A was identical with that of authentic squalene. Peak B showed a molecular ion at *m/e* 438 corresponding to $C_{32}H_{54}$ with a relative intensity of 1.5% of the base peak at *m/e* 83. The peak at *m/e* 83 can be reasonably assigned to $[C_2H_5C(CH_3)=CHCH_2]^+$ which is a homolog of $[CH_3C(CH_3)=CHCH_2]^+$, *m/e* 69, observed as the base peak in the spectrum of squalene. Peaks were also observed at *m/e* 355 (M − 83), 219 [M − (83 + 68 × 2)], 151 (83 + 68), and 95, with relative abundances of 3.1, 0.8, 12.3, and 21.5%, respectively. These values can be explained as homologous fragments corresponding to the peaks at *m/e* 341, 205, 137, and 81 in the spectrum of squalene. These results indicate that homofarnesyl-PP (1) is enzymically converted into bishomosqualene (5).



5 : $R_1=C_2H_5$, $R_2=CH_3$
6 : $R_1=CH_3$, $R_2=C_2H_5$

A homosqualene (1-methylsqualene, $C_{31}H_{52}$) which might be formed as a result of asymmetric condensation between 1 and farnesyl-PP, if present endogenously in the microsomes, was not included in the reaction products. This fact suggests that farnesyl-PP was absent in the microsomes used and that the presence of squalene in the products did not result from the *de novo* synthesis from farnesyl-PP during the incubation.

The enzymic reaction of 2 was similar to that of 1, affording a squalene-like hydrocarbon. The chromatographic property of this hydrocarbon was identical with that of the product derived from 1, and it must be an isomeric bishomosqualene 6.

The ethyl homologs 3 and 4, however, did not give any squalene-like material, but the whole radioactivity in the petroleum extracts was found in the corresponding alcohols formed by the hydrolysis probably due to phosphatase present in the microsomes.

(5) DeW. S. Goodman and G. Popják, *J. Lipid Res.*, 1, 286 (1960).

(6) A Shimadzu Radiogaschromatograph RID 2E was used.

(7) A Hitachi GC-MS spectrometer RMU-6GC was used. The glpc was carried out with a 1-m column of 2% OV-17 at 250°.

Acknowledgment. We thank Mr. H. Sato, Naka Works, Hitachi, Ltd. for the measurement of the glpc–mass spectra.

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Intramolecular and Intermolecular Oxidative Coupling Reactions by a New Iron Complex $[Fe(DMF)_3Cl_2][FeCl_4]$

Sir:

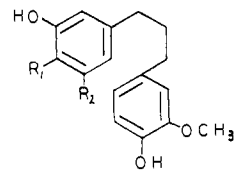
It has been known for a long time that phenols are readily oxidized by many different reagents. The products are mostly complicated mixtures of dimeric, polymeric, and quinoid compounds in nature. Oxidative phenol coupling has received considerable attention owing both to its utility as a synthetic reaction and its proposed involvement in the biosyntheses of a number of classes of natural products.[1] To date, various oxidizing agents have been investigated but with limited success;[2] we wish to report a new method for intramolecular and intermolecular oxidative coupling by a new complex prepared from ferric chloride and dimethylformamide (DMF) which gives the oxidation products in high yield under mild conditions and which avoids the formation of polymeric compounds in minimum amounts.

After trying a variety of oxidizing agents under various conditions we found ferric chloride in DMF led to fairly good results for the oxidation of compounds of type **1**. During further investigation of these reactions, a new complex[3] which has the molecular formula $[Fe(DMF)_3Cl_2][FeCl_4]$ and which is responsible for the phenol oxidation, was isolated. These observations prompted us to investigate the use of this complex for the oxidative coupling reactions in detail.

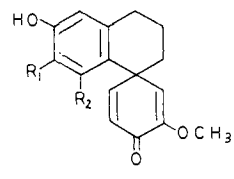
The oxidizing reagent was prepared as follows. To a solution of ferric chloride, 163 g (1 mol) in 1.6 l. of dry ether, DMF, 110 g (1.5 mol), was added with stirring. A precipitate (260 g, 95.2% yield) was obtained as a yellowish green powder[4] which was not hygroscopic and which could be recrystallized from methylene chloride and ethanol to give needles,[5] mp 220° (*Anal.* Found: C, 19.65; H, 3.94; N, 7.57; Cl, 39.38). The visible light absorption spectra of this complex either in the solid state or in the solution of nonaqueous solvents show the characteristic absorption at 530 mμ due to the $FeCl_4^-$ ion.[6] These observations reduce to the molecular formula $[Fe(DMF)_3Cl_2][FeCl_4]$ for this complex.

A typical oxidative coupling reaction using a new complex was carried out in the following manner. 1-(3,4-Dimethoxy-5-hydroxyphenyl)-3-(3-methoxy-4-hydroxyphenyl)propane (**1**) ($R_1 = R_2 = OCH_3$), bp 194–197° (0.3 mm), was prepared from the corresponding chalcone. To a solution of the complex, 5.44 g (10 mmol) in 55 ml of water, 0.318 g (1 mmol) of **1** ($R_1 = R_2 = OCH_3$) in 10 ml of ether was added and the mixture was refluxed with stirring for 1 hr. The dienone **2** ($R_1 = R_2 = OCH_3$) (mp 245–247°; ir (KBr) 3.17, 6.06, 6.13 μ; uv (C_2H_5OH) 234 (ε 17,060), 280 mμ (ε 8090)) was obtained as a crystalline precipitate in 67% yield.[7] In the same manner, by the oxidation of **1** ($R_1 = OCH_3$; $R_2 = H$), mp 103–104°, the dienone **2** ($R_1 = OCH_3$, $R_2 = H$[8]), mp 162–163°, was formed in high yield (67%), and similarly the oxidation of **1** ($R_1 = R_2 = H$), mp 58–58.5°, produced the dienone **2** ($R_1 = R_2 = H$), mp 158–160°, in 39% yield.

To illustrate additional examples, the following intermolecular oxidative coupling by the new complex was investigated. The oxidation of *p*-cresol[9] afforded only Pummerer's ketone **3** in 28% yield[7] and the oxidation of ferulic acid[10] produced a dilactone **4** in 35% yield, under similar reaction conditions. The oxidation of methyl indole-3-acetate gave an unsymmetrical coupling product **5** ($R_1 = CH_3$; $R_2 = CO_2CH_3$): mp



1



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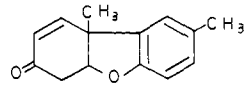
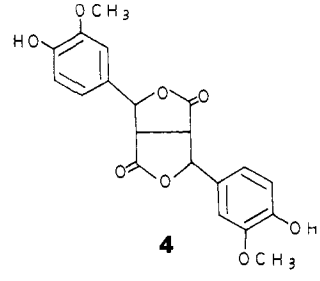


3



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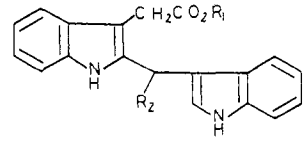

5

136–138°; nmr ($CDCl_3$) δ 3.58 and 3.70 (each s), 3.81 (s, 2 H), 5.63 (s, 1 H), 6.87 (1 H), 6.95–7.35 (m, 6 H), 7.39–7.70 (m, 2 H), 8.20 and 8.85 (each 1 H), in 50%

(1) W. I. Taylor and A. R. Battersby, Ed., "Oxidative Coupling of Phenols," Marcel Dekker, New York, N. Y., 1967.

(2) For recent examples, the following reagents were applied for the oxidative phenol coupling: (a) vanadium oxytrichloride and vanadium tetrachloride; W. L. Carrick, G. L. Karapinka, and G. T. Kwiatkowski, *J. Org. Chem.*, **34**, 2388 (1969); M. A. Schwartz, R. A. Holton, and S. W. Scott, *J. Amer. Chem. Soc.*, **91**, 2800 (1969); (b) manganic tris(acetylacetonate); M. J. S. Dewar and T. Nakaya, *J. Amer. Chem. Soc.*, **90**, 7134 (1968).

(3) The formation of solvates in the reactions between DMF and various metal salts including ferric chloride is known: R. C. Poul and R. B. Sreenathan, *Indian J. Chem.*, **4**, 382 (1966); B. S. Magor and T. D. Smith, *J. Chem. Soc. A*, 1753 (1968); N. N. Dass and M. H. George, *J. Polym. Sci., Part A-1*, 269 (1969).

(4) It was a mild, exothermic reaction. The precipitate is sufficiently pure to use directly for oxidation reactions.

(5) It is a remarkable feature of this complex that it is unchanged upon recrystallization from water or acetonitrile.

(6) D. W. Meek and R. S. Drago, *J. Amer. Chem. Soc.*, **83**, 4322 (1961).

(7) The mother solution consisted mainly of starting material.

(8) The nmr spectrum of **2** ($R_1 = OCH_3$; $R_2 = H$) exhibited aromatic proton absorption consistent with a 2,4,5-trisubstituted phenol moiety, thus establishing **2** as the para–para coupling product.

(9) C. G. Hayne, A. H. Turner and W. A. Waters, *J. Chem. Soc.*, 2823 (1956); T. Kametani and K. Ogasawara, *Chem. Pharm. Bull.*, **16**, 1138 (1968).

(10) K. Freudenberg and H. Dietrich, *Chem. Ber.*, **86**, 1157 (1953); N. J. Cartwright and R. D. Haworth, *J. Chem. Soc.*, 535 (1944).